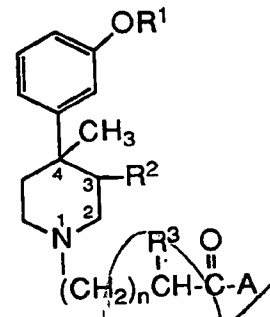
Claims:

1. A trans-3,4 isomer of a compound of the formula (I)



(I)

wherein:

R^1 is hydrogen or C_1-C_5 alkyl;

R^2 is hydrogen, C_1-C_5 alkyl or C_2-C_6 alkenyl;

R^3 is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, phenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl or phenyl-substituted C_1-C_3 alkyl;

A is OR^4 or NR^5R^6;

wherein:

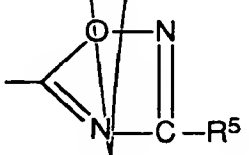
R^4 is hydrogen, C_1-C_{10} alkyl C_2-C_{10} alkenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl or phenyl-subsituted C_1-C_3 alkyl;

R^5 is hydrogen or C_1-C_3 alkyl;

R^6 is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, cycloalkyl, phenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl, phenyl-substituted C_1-C_3 alkyl, or $(CH_2)_q$-B; or

R^5 and R^6 are each CH_2 which together with N form a 4 to 6-membered heterocyclic ring;

wherein:

B is  CW or NR^7R^8;

wherein:

R^7 is hydrogen or C_1-C_3 alkyl;

R^8 is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, cycloalkyl-substituted C_1-C_3 alkyl, cycloalkyl, C_5-C_8 cycloalkenyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl, phenyl or phenyl-substituted C_1-C_3 alkyl; or

R^7 and R^8 are each CH_2 which together with N form a 4- to 6-membered heterocyclic ring;

W is OR^9, $NR^{10}R^{11}$, or OE;

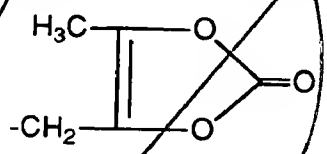
wherein:

R^9 is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl or phenyl-substituted C_1-C_3 alkyl;

R^{10} is hydrogen or C_1-C_3 alkyl;

R^{11} is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, phenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, phenyl-substituted C_1-C_3 alkyl, or $(CH_2)_m\overset{O}{\overset{\|}{C}}Y$; or

R^{10} and R^{11} are each CH_2 which together with N form a 4- to 6-membered heterocyclic ring;

E is $(CH_2)_m\overset{O}{\overset{\|}{C}}$-D,  , or $-R^{12}-O\overset{O}{\overset{\|}{C}}R^{13}$

wherein:

R^{12} is C_1-C_3 alkyl substituted methylene,

R^{13} is C_1-C_{10} alkyl;

D is OR^{14} or $NR^{15}R^{16}$;

wherein:

R^{14} is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, or C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl or phenyl-substituted C_1-C_3 alkyl;

R^{15} is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, phenyl, phenyl-substituted C_1-C_3 alkyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl or C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl;

R^{16} is hydrogen or C_1-C_3 alkyl;

R^{15} and R^{16} are each CH_2 which together with N form a 4- to 6-membered heterocyclic ring;

Y is OR^{17} or $NR^{18}R^{19}$;

wherein:

R^{17} is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl, or phenyl-substituted C_1-C_3 alkyl;

R^{18} is hydrogen or C_1-C_3 alkyl;

R^{19} is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, phenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl, or phenyl-substituted C_1-C_3 alkyl; or

R^{18} and R^{19} are each CH_2 which together with N form a 4- to 6-membered heterocyclic ring;

n is 0-4;

q is 1-4;

m is 1-4;

or pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein R^1 is hydrogen; R^2 is C_1-C_3 alkyl; n = 1 or 2; and R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl.

3. The compound of claim 2 wherein A is OR^4 and R^4 is hydrogen or C_1-C_3 alkyl.

4. The compound of claim 2 wherein A is NR^5R^6 in which R^5 is hydrogen and R^6 is $(CH_2)_q$-B wherein q is 1 to 3 and B is -C(O)W.

5. The compound of claim 4 wherein W is OR^9 and R^9 is hydrogen, C_1-C_5 alkyl, phenyl-substituted C_1-C_2 alkyl, C_5-C_6 cycloalkyl, or C_5-C_6 cycloalkyl-substituted C_1-C_3 alkyl.

6. The compound of claim 4 wherein W is $NR^{10}R^{11}$ in which R^{10} is hydrogen or C_1-C_3 alkyl, and R^{11} is hydrogen, C_1-C_3 alkyl or $(CH_2)_m C(O)Y$.

7. The compound of Claim 6 wherein m is 1 to 3 and Y is OR^{17} or $NR^{18}R^{19}$ wherein R^{17}, R^{18} and R^{19} are independently hydrogen or C_1-C_3 alkyl.

8. The compound of Claim 4 wherein W is $OCH_2C(O)OD$ in which D is OR^{14} or $NR^{15}R^{16}$ wherein R^{14} is hydrogen or C_1-C_3 alkyl, R^{15} is hydrogen and R^{16} is methyl or benzyl.

9. The compound of Claim 4 wherein W is $OR^{12}O\ C(O)R^{13}$, wherein R^{12} is $-CH(CH_3)-$ or $-CH(CH_2CH_3)-$ and R^{13} is C_1-C_3 alkyl.

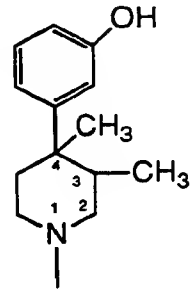
10. The compound of Claim 1 wherein the configuration at positions 3 and 4 of the piperidine ring is each R.

11. A compound of Claim 1 selected from the group consisting of $QCH_2CH[CH_2(C_6H_5)]C(O)OH$, $QCH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OCH_2CH_2$, $QCH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OH$, $Q\text{-}CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_3$, $Q\text{-}CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_2CH_3$, $G\text{-}NH(CH_2)_2C(O)NH_2$, $G\text{-}NH(CH_2)_2C(O)NHCH_3$, $G\text{-}NHCH_2C(O)NH_2$, $G\text{-}NHCH_2C(O)NHCH_3$, $G\text{-}NHCH_2C(O)NHCH_2CH_3$, $G\text{-}NH(CH_2)_3C(O)OCH_2CH_3$, $G\text{-}NH(CH_2)_3C(O)NHCH_3$, $G\text{-}NH(CH_2)_2C(O)OH$, $G\text{-}NH(CH_2)_3C(O)OH$, $QCH_2CH[CH_2(C_6H_{11})]C(O)NHCH_2C(O)OH$, $QCH_2CH[CH_2(C_6H_{11})]C(O)NH(CH_2)_2C(O)OH$, $QCH_2CH[CH_2(C_6H_{11})]C(O)NH(CH_2)_2C(O)NH_2$, $Z\text{-}NHCH_2C(O)OCH_2CH_3$, $Z\text{-}NHCH_2C(O)OH$, $Z\text{-}NHCH_2C(O)NH_2$, $Z\text{-}NHCH_2C(O)N(CH_3)_2$, $Z\text{-}NHCH_2C(O)NHCH(CH_3)_2$, $Z\text{-}NHCH_2C(O)OCH_2CH(CH_3)_2$, $Z\text{-}NH(CH_2)_2C(O)OCH_2(C_6H_5)$, $Z\text{-}NH(CH_2)_2C(O)OH$, $Z\text{-}NH(CH_2)_2C(O)NHCH_2CH_3$, $Z\text{-}NH(CH_2)_3C(O)NHCH_3$, $Z\text{-}NHCH_2C(O)NHCH_2C(O)OH$, $Z\text{-}NHCH_2C(O)OCH_2C(O)OCH_3$, $Z\text{-}NHCH_2C(O)O(CH_2)_4CH_3$, $Z\text{-}NHCH_2C(O)OCH_2C(O)NHCH_3$, $Z\text{-}NHCH_2C(O)O\text{-}$

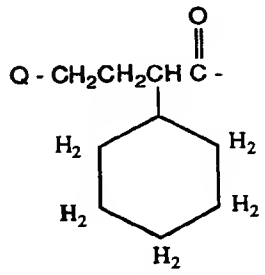
(4-methoxycyclohexyl), Z-$NHCH_2C(O)OCH_2C(O)NHCH_2(C_6H_5)$, and Z-$NHCH_2C(O)OCH(CH_3)OC(O)CH_3$,

wherein:

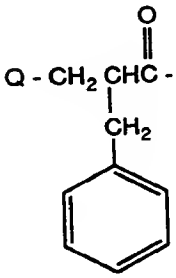
Q represents trans-3,4-dimethyl



G represents



and Z represents



and pharmaceutically acceptable salts thereof.

12. A compound of claim 11 selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)Z-$NHCH_2C(O)OH$, (-)Z-$NHCH_2C(O)OH$, (3R,4R,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,S)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3R,4R)-$ZNHCH_2C(O)NHCH_2(C_6H_5)$ and (3R,4R)-G-$NH(CH_2)_3C(O)OH$, and pharmaceutically acceptable salts thereof.

13. A substantially pure stereoisomer of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical formulation comprising a compound of Claim 1 or the salt thereof in combination with a pharmaceutically acceptable excipient.

15. A pharmaceutical formulation comprising a compound of Claim 11 or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable excipient.

16. A method for treating irritable bowel syndrome in a patient said method comprising administering to said patient an effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

17. A method for treating a peripheral effect of an opioid in a patient which comprises administering to said patient an effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

18. The method of Claim 17 wherein said peripheral effect being treated is constipation, nausea or vomiting.

19. A method for blocking mu receptors in mammals comprising administering to a mammal requiring blocking of a mu receptor a receptor blocking dose of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

20. A method for treating idiopathic constipation in a patient said method comprising administering to said patient an effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.